From: Brookmire, Lauren
To: Choudhuri, Supratim; Mattia, Antonia; Merker, Robert I; Srinivasan, Jannavi
Subject: RE: Letter to FDA Re Dosing for 28-Day Study
Date: Wednesday, September 07, 2016 12:07:33 PM

Thank you, Toni and Supratim. I agree that the context of our response should emphasize the fact that we cannot offer the assurances in which this letter is hoping to obtain (confirmation that their not-yet-conducted study will support the safety of their GRAS claim). We can throw in some specific comments as well.

I feel that these are some additional important points to remember:

- Based on our meeting with the company this past spring, the current "soy leghemoglobin product" is NOT the same as the one reviewed in GRN 0540. The composition of the substance is not the same as what we originally reviewed.
- The Impossible Burger (which contains the substance) went on the market in New York this past July. I question why the safety studies were not conducted first.
- I got the impression this past spring that they will NOT be submitting a new GRN to FDA, but instead they are performing their own internal GRAS conclusion themselves. The consulting through Gary is to help build their internal documentation.

Bob suggested meeting tomorrow to make sure that we are all on the same page. I will have an email response drafted beforehand, in hopes of keeping this meeting to 15 minutes or so. I will look for a time on calendars that works for everyone.

Thank you all for your time and input,
Lauren

From: Choudhuri, Supratim
Sent: Wednesday, September 07, 2016 11:47 AM
To: Mattia, Antonia; Merker, Robert I; Brookmire, Lauren; Srinivasan, Jannavi
Subject: RE: Letter to FDA Re Dosing for 28-Day Study

The proposal of a 28-day study came from Gary Yingling at the meeting. We never suggested it. We emphasized on digestibility, bioinformatics analysis, narrative on soy allergy etc.

However, just like we do not suggest a notifier what experiment to run, we should not suggest the notifier not to run an experiment if the notifier/agent proposed it in the first place, even after listening to the scientific discussion at length. So, the 28-day study is still on.

In my email to Lauren, I expressed one opinion, which is logical to express. That is, *the dose should not be MTD*. But, with regard to the suitability of the highest dose proposed, my opinion followed the GRAS opinion format, that is, *based on the rationale Gary provided for choosing the highest dose, I do not have any question at this time*

From: Mattia, Antonia
Sent: Wednesday, September 07, 2016 11:35 AM
To: Merker, Robert I; Choudhuri, Supratim; Brookmire, Lauren; Srinivasan, Jannavi
Subject: FW: Letter to FDA Re Dosing for 28-Day Study

Bob has a point. I wasn't at the meeting so I don't know what we recommended regarding a toxicology study or studies. However, the intent of my note was to caution you in general about offering assurances to a notifier that a not-yet-conducted study will get them to GRAS. And, I wanted to point out other general considerations about dose selection and margin of safety considerations when it comes to a shorter study (such as a 28-d vs. a 90-d study) and the potential for exposure to increase. Although I did not intend to address whether the study was needed, or not, if they are willing to do the study I would not discourage it.

Toxicology should respond as well.

From: Merker, Robert I
Sent: Wednesday, September 07, 2016 9:32 AM
To: Choudhuri, Supratim; Mattia, Antonia; Brookmire, Lauren; Srinivasan, Jannavi
Cc: Dinovi, Michael J
Subject: RE: Letter to FDA Re Dosing for 28-Day Study

Good morning,
Not to be contrary and question my toxicologist friends, but I think that based on what we know about proteins, why is a feeding study needed? Why is much more needed than digestibility and comparison with sequences of known toxic/allergenic proteins. It's going to be labeled, so if there is sequence homology to soy proteins, that shouldn't be an issue. I don't think we recommended a feeding study at the meeting.
Bob

From: Choudhuri, Supratim
Sent: Tuesday, September 06, 2016 5:15 PM
To: Mattia, Antonia; Brookmire, Lauren; Srinivasan, Jannavi
Cc: Merker, Robert I; Dinovi, Michael J
Subject: RE: Letter to FDA Re Dosing for 28-Day Study

Thanks Toni.

From: Mattia, Antonia
Sent: Tuesday, September 06, 2016 5:14 PM
To: Choudhuri, Supratim; Brookmire, Lauren; Srinivasan, Jannavi
Cc: Merker, Robert I; Dinovi, Michael J
Subject: RE: Letter to FDA Re Dosing for 28-Day Study

And, a 90 day study would be better…..you can repeat that suggestion, which I take it was already

made at a presub meeting.

From: Mattia, Antonia
Sent: Tuesday, September 06, 2016 5:08 PM
To: Choudhuri, Supratim; Brookmire, Lauren; Srinivasan, Jannavi
Cc: Merker, Robert I; Dinovi, Michael J
Subject: RE: Letter to FDA Re Dosing for 28-Day Study

Here's what we need to respond to…." We are now seeking confirmation from the Agency that this dose schedule is acceptable, and would support the safety of the product in a future GRAS notification."

I don't think we want to put ourselves in the position of saying that we confirm that the dosing would support the safety of the product in a future GRAS notice. We can comment that their rationale makes sense so long as no effects are observed in the study and the estimate of exposure that they are using is reasonable and doesn't change. Telling a notifier that a study --- not yet conducted --- would support a GRAS conclusion puts us on a slippery slope. We can't offer such assurances in advance of the conduct of the study so be careful in how you respond to Mr. Yingling.

From: Choudhuri, Supratim
Sent: Wednesday, August 31, 2016 6:27 PM
To: Brookmire, Lauren; Srinivasan, Jannavi
Cc: Merker, Robert I; Mattia, Antonia; Dinovi, Michael J
Subject: RE: Letter to FDA Re Dosing for 28-Day Study

Hi Lauren:

As you know, we do not suggest the notifier what study to perform or how to conduct the study. As you also remember, Gary Yingling proposed this 28-day study during our meeting. The suggestion did not come from FDA.

So, Gary/the notifier has developed a rationale for choosing the highest dose for the study (100-times the intended 90th percentile estimated daily intake calculations). This dose is not intended to be the maximum tolerated dose (MTD).

My opinion is as follows:

1. I agree with the fact that this dose should not be the MTD.
2. Based on the rationale Gary provided for choosing the highest dose, I do not have any question at this time.

Feel free to check with Bob, Mike, Toni if you want to, before conveying this to Gary.

Thanks

Supratim

From: Brookmire, Lauren
Sent: Wednesday, August 31, 2016 5:16 PM
To: Choudhuri, Supratim; Srinivasan, Jannavi
Cc: Merker, Robert I; Mattia, Antonia; Dinovi, Michael J
Subject: FW: Letter to FDA Re Dosing for 28-Day Study

Hi Supratim and Jannavi,

I received the attached letter from Gary Yingling while I was out on vacation. I will speak with Bob and/or other management on the appropriate way to respond. I imagine this may involve feedback from you two, as you were the technical reviewers for GRN 0540.

I have CC'd Toni and Mike (acting DD) to keep them in the loop.

Thank you,
Lauren

From: Yingling, Gary L. [redacted]
Sent: Tuesday, August 23, 2016 11:27 AM
To: Brookmire, Lauren
Cc: Merker, Robert I; Vaughn, Jessica L.
Subject: Letter to FDA Re Dosing for 28-Day Study

Dear Lauren: Attached is a letter requesting comment on the intent of Impossible Foods to use the doses of 250, 500 and 750 mg/kg bw/day in the 28 day feeding study. A quick response would be most appreciated. gary

Gary L. Yingling
Morgan, Lewis & Bockius LLP
[redacted]